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The monocyte/high-density lipoprotein cholesterol ratio in patients with primary hypolipoproteinemia

Primer hipolipoproteinemili hastalarda monosit/yüksek yoğunluklu lipoprotein kolesterol oranı

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ABSTRACT

Aim: Hypolipoproteinemia is low blood lipid levels in adults. Primary hypolipoproteinemia due to genetic mutations is a rare condition. Studies to demonstrate the clinical significance of hypolipoproteinemia are limited. It was aimed to evaluate the clinical and laboratory characteristics of patients with primary hypolipoproteinemia and the monocyte/high-density lipoprotein (HDL) ratio in this study.

Material and Method: Eight patients with primary hypolipoproteinemia and twelve healthy control subjects were compared in terms of lipid profiles, monocyte/HDL ratios, hemogram, acute phase response tests, and liver tests.

Results: Triglycerides (TG), low-density lipoprotein (LDL), and total cholesterol (TC) levels were found to be significantly lower in the patient group than in the control group (p=0.037 and <0.001 for LDL and TC both, respectively). There was no difference between the groups in terms of HDL levels. Lipoprotein (a) (Lp(a)) levels were found to be significantly lower in the patient group compared to the control group (p=0.006). Absolute monocyte count (AMC) was found to be significantly higher in the patient group than in the control group (p=0.002). Monocyte/HDL ratios (MHR) were significantly higher in the patient group than in the control group (p=0.016). There was a negative correlation between MHR and LDL (p=0.001).

Conclusion: AMC and MHR were found higher in patients with primary hypolipoproteinemia than in the healthy control group in this study. Monocytes are involved in all stages of the progression of atherosclerotic disease. HDL is known to have a protective role in atherosclerotic diseases with its anti-inflammatory and antioxidant effects. MHR, which is an index that combines both, has been shown to be a prognostic marker in cardiovascular diseases. This study is the first to investigate MHR in primary hypolipoproteinemia patients. Despite the small sample size and the heterogeneous nature of the patients included high AMC and MHR levels are important findings of the current study. Although patients with hypolipoproteinemia are attributed to a low risk for atherosclerotic diseases, high AMC and MHR are a warning that these patients should be followed carefully due to changes in lipid redistribution in terms of the risk of atherosclerotic disease.

Keywords: Hypolipoproteinemias, hypobetalipoproteinemias, lipoprotein(a), monocytes, non-alcoholic fatty liver disease

ÖZ

Amaç: Hipolipoproteinemi erişkinlerde kan lipid düzeylerindeki düşüklüktür. Genetik mutasyonlara bağlı primer hipolipoproteinemi nadir görülen bir durumdur. Hipolipoproteineminin klinik önemini gösteren çalışmalar sınırlıdır. Bu çalışmada primer hipolipoproteinemili hastaların klinik ve laboratuvar özelliklerinin ve monosit/yüksek yoğunluklu lipoprotein (HDL) oranının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Primer hipolipoproteinemili sekiz hasta ile on iki sağlıklı kontrol grubunun lipid profilleri, monosit/HDL oranları, hemogram, akut faz yanıt testleri ve karaciğer testleri karşılaştırıldı.

Bulgular: Trigliserid (TG), düşük yoğunluklu lipoprotein (LDL) ve total kolesterol (TK) düzeyleri hasta grubunda kontrol grubuna göre anlamlı derecede düşük bulundu (sırasıyla p=0,037 ve LDL ve TK'nın her ikisi için <0,001). HDL düzeyleri açısından gruplar arasında fark yoktu. Lipoprotein (a) (Lp(a)) düzeyleri hasta grubunda kontrol grubuna göre anlamlı derecede düşük bulundu (p=0,006). Absolü monosit sayısı (AMS) hasta grubunda kontrol grubuna göre anlamlı olarak yüksek bulundu (p=0,002). Monosit/HDL oranları (MHO) hasta grubunda kontrol grubuna göre anlamlı derecede yüksekti (p=0,016). MHO ile LDL arasında negatif korelasyon saptandı (p=0,001).

Sonuç: Bu çalışmada primer hipolipoproteinemili hastalarda AMS ve MHO sağlıklı kontrol grubuna göre daha yüksek bulundu. Monositler, aterosklerotik hastalığın ilerlemesinin tüm aşamalarında yer alır. HDL'nin antiinflamatuar ve antioksidan etkileri ile aterosklerotik hastalıklarda koruyucu rolü olduğu bilinmektedir. Her ikisini birleştiren bir indeks olan MHR'nin kardiyovasküler hastalıklarda prognostik bir belirteç olduğu gösterilmiştir. Bilindiği kadarıyla bu çalışma, primer hipolipoproteinemi hastalarında MHO'yu araştıran ilk çalışmadır. Küçük örneklem büyüklüğüne ve dahil edilen hastaların heterojen doğasına rağmen yüksek AMS ve MHO düzeyleri mevcut çalışmanın en önemli bulgularıdır. Hipolipoproteinemili hastalara aterosklerotik hastalıklar için düşük risk atfedilmesine rağmen, yüksek AMS ve MHO, aterosklerotik hastalık riski açısından lipid redistribüsyonundaki değişiklikler nedeniyle bu hastaların dikkatle izlenmesi gerektiğine dair bir uyarı niteliğindedir.

Anahtar Kelimeler: Hipolipoproteinemiler, hipobetalipoproteinemiler, lipoprotein(a), monositler, non alkolik yağlı karaciğer hastalığı

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INTRODUCTION

Hypolipoproteinemia (hypolipidemia or hypocholesterolemia) is low blood lipid levels in adults, usually detected during routine lipid profile screening. Although it is not very common, it usually occurs due to secondary causes. Causes of secondary hypolipoproteinemia include solid and hematological malignancies, infections, critical diseases like sepsis or other conditions requiring hospitalization in the intensive care unit, malnutrition and malabsorption, liver parenchymal diseases, neuropsychiatric diseases, and thyrotoxicosis (1). Also, there are genetic conditions that cause low cholesterol. The hereditary causes of primary hypolipoproteinemia are genetic mutations in cholesterol absorption, biosynthesis, or metabolism.

The causes of hereditary hypolipoproteinemia include mainly abetalipoproteinemia, familial hypobetalipoproteinemia, familial combined hypolipidemia, chylomicron retention disease, and familial hypoalphalipoproteinemia. In abetalipoproteinemia, low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apo B) are at levels that cannot be measured. There is a mutation in the microsomal transfer protein (MTP) gene and it is inherited autosomal recessively (2). Patients are usually diagnosed with failure to thrive, steatorrhea, and conditions related to deficiencies of fat-soluble vitamins in childhood. Chylomicron retention disease is usually diagnosed in childhood with similar clinical findings. There is a mutation in the Sar1b gene, it is inherited autosomal recessively. Besides LDL-C, high-density lipoprotein cholesterol (HDL-C) is also low (3).

There are various mutations in the APOB gene in hypobetalipoproteinemia, and it has an autosomal dominant inheritance pattern. Homozygous hypobetalipoproteinemia clinically is similar to abetalipoproteinemia. Heterozygous familial hypobetalipoproteinemia is usually diagnosed during routine lipid profile screening or while investigating the etiology of non-alcoholic fatty liver disease (NAFLD) (4). LDL-C and apo B plasma concentrations are decreased in these patients. Some patients may experience deficiencies in fat-soluble vitamins (5).

In familial hypoalphalipoproteinemia, apolipoprotein A1 (apo A1) deficiency and low HDL-C are observed. While patients with low HDL due to acquired causes are at risk for early-onset coronary artery disease and cerebrovascular disease, there is not enough literature data on the risk status for atherosclerotic diseases since familial hypoalphalipoproteinemia is not a common condition (6).

Loss-of-function mutations in the angiopoietin-like protein 3 (ANGPTL3) gene are involved in familial combined hypolipidemia. It is inherited autosomal recessively, there is a decrease in lipoproteins such as very-low-density lipoprotein (VLDL) and LDL containing apo B, as well as a low level of HDL containing apo A1 (7).

In contrast to hypercholesterolemia, the causes of hypocholesterolemia and its consequences on morbidity have not been adequately studied in clinical practice. Even if primary hypolipoproteinemia is not a common condition, it is important because it must be differentiated from secondary causes and it requires follow-up in terms of pathologies that may occur in lipid metabolism related to the underlying genetic mutation. In addition, it is another important point to raise the awareness of clinicians in terms of the necessity of referral to genetic counseling in order to avoid the risks of severe fat malabsorption and related developmental, neurological, and ophthalmological complications in the children of the affected individual depending on the inheritance pattern.

Studies to demonstrate the clinical significance of hypolipoproteinemia are limited and are generally associated with fat-soluble vitamin deficiencies, atherosclerotic diseases, and NAFLD (8). Contrary to the hypercholesterolemia associated with hyperinflammation, there are no adequate studies on whether inflammation is suppressed in patients with hypolipoproteinemia. In this study, it was aimed to evaluate the clinical and laboratory characteristics of patients with primary hypolipoproteinemia and the monocyte/HDL ratio, which is one of the indicators of inflammation associated with atherosclerosis.

MATERIAL AND METHOD

The study was carried out with the permission of Eskisehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 26.07.2022, Decision No: 35). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study is retrospective and observational in nature. Eight patients without consanguinity, whose lipid profile was evaluated and hypolipidemia was detected in their application to the Internal Medicine outpatient clinic of our hospital were included. Secondary causes of hypolipidemia were excluded. A control group consisted of 12 healthy individuals who had applied for routine health check-ups, were age and gender matched, had no family history of hypolipidemia, had no chronic disease, had no history of using lipid-lowering therapy, and had their lipid profile measured.

Blood samples of the patients were obtained in the morning after at least 8 hours of fasting. The measurements of triglycerides (TG), HDL-C, LDL-C, total cholesterol (TC), and gamma glutamyl transferase (GGT) were made by enzymatic colorimetric method; lipoprotein (a) (Lp(a)) by particle enhanced immunoturbidimetric method; Apo A1 and Apo B, and serum C-reactive protein

(CRP) by immunoturbidimetric method; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by spectrophotometric method; alkaline phosphatase (ALP) by colorimetric method. Roche Cobas 702 device was used for these analyses. Complete blood count parameters were determined on a Sysmex XN 9100 hematology analyzer. Erythrocyte sedimentation rate (ESR) was studied in a fully automated Vacuplus ESR-120 analyzer by the Westergren method.

Statistical Analysis

Continuous data are given as mean±standard deviation. Categorical data are given as a percentage (%). The Shapiro Wilk test was used to investigate the suitability of the data for normal distribution. In the comparison of normally distributed groups, independent sample t-test analysis was used. The Mann-Whitney U test was used for the comparison of groups that did not conform to the normal distribution. Spearman correlation coefficients were calculated to determine the direction and size of the relationship (correlation) between variables, due to the small sample size. Pearson Exact Chi-Square analyzes were used in the analysis of the created cross tables. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used in the analysis. A value of $p<0.05$ was accepted as a criterion for statistical significance.

RESULTS

The mean age of the patient group (n=8) was 51.9±18.6, and the mean age of the control group (n=12) was 52.8±15.5. The patient group consisted of five men and three women, and the control group consisted of five men and seven women. The groups were statistically similar in terms of age and gender.

In the comparison of the lipid profiles between the groups, TG, LDL, and TC levels were found to be significantly lower in the patient group than in the control group (p=0.037 and <0.001 for LDL and TC both, respectively). There was no difference between the groups in terms of HDL levels. Among all participants, only one person from the patient group had a high Lp(a) level, while Lp(a) levels were within the reference ranges in the other participants. Lp(a) levels were found to be significantly lower in the patient group (n=7) compared to the control group (p=0.006) when the groups were compared excluding the patient with elevated Lp(a) levels from the evaluation.

In the evaluation of hemogram parameters, no difference was found between the groups in terms of hemoglobin, red cell distribution width (RDW), white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count (Plt) and mean platelet volume (MPV). Absolute monocyte count (AMC) was found to be significantly higher in the patient group than in the control group (p=0.002). When the monocyte/HDL ratios (MHR) were compared, significantly higher rates were found in the patient group than in the control group (p=0.016). There was a negative correlation between MHR and LDL (p=0.001). The acute phase response tests ESR and CRP were similar between the groups.

AST, ALT, GGT, and ALP levels were within reference ranges in both the patient and control groups, and there was no statistical difference between the groups. The median of 25 hydroxy vitamin D levels was consistent with a mild deficiency in both groups, and no significant difference was found between the groups. The comparison of the laboratory tests of the patient and control groups and the p values are given in **Table**.

Table. The demographic characteristics and laboratory parameters of the patient and control groups

	Patients (n: 8)	Healthy controls (n: 12)	p
Age (years)	51.9±18.6	52.8±15.5	0.817*
Gender			0.648
Male	5 (62%)	5 (42%)	
Female	3 (38%)	7 (58%)	
TG (mg/dl)	39.5 (32.3-99.8)	115 (100-137)	**<0.0372****
HDL (mg/dl)	46.9±22	53.8±13.3	0.537*
LDL (mg/dl)	32.9±20.8	119±26.3	**<0.001***
TC (mg/dl)	102±23.6	189±28.6	**<0.001***
Lp(a) (nmol/L)	7.4 (2.3-8.1)	21.4 (12.1-29.4)	**0.0068****
ESR (mm/h)	15±6.12	12.7±8.85	0.333*
CRP (mg/L)	1.6 (1-2)	1.85 (1.2-2.6)	0.509**
Hb (g/dl)	14 (13.8-14.2)	14.2 (13.5-15.1)	0.436**
RDW (%)	12.8 (12.1-13.9)	12.9 (12.6-13.7)	0.67**
WBC (#/uL)	7450 (5050-7880)	5450 (4780-7650)	0.757**
ANC (#/uL)	3930±1400	3910±1760	1*
ALC (#/uL)	1910±645	1910±548	0.786*
AMC (#/uL)	565±113	410±66.9	**0.0025***
MHR	11.9 (8.87-16.2)	6.94 (6.44-9.31)	**0.0168****
Platelet (10^3/uL)	253±24.4	287±83.9	0.247*
MPV (fL)	10.3±0.814	9.83±0.881	0.315*
AST (U/L)	19 (17.8-23.3)	16.5 (14.8-20.3)	0.122**
ALT (U/L)	18.5 (15.3-20.8)	19.5 (16.8-24.3)	0.671**
ALP (U/L)	74.1±19	93.9±30.1	0.063*
GGT (IU/L)	18 (17.8-26.5)	26 (15.8-38.3)	0.699**
25-OH-D (ng/ml)	21 (15.4-28.6)	23 (17.5-25.5)	0.908**

TG: triglycerides (40-205 mg/dl), HDL: high-density lipoprotein (34-82 mg/dl), LDL: low-density lipoprotein (75-172 mg/dl), TC: total cholesterol (139-249 mg/dl), Lp(a): Lipoprotein(a) (0-75 nmol/L) , ESR: erythrocyte sedimentation rate (0-20 mm/h), CRP: C-reactive protein (0-5 mg/L), Hb: hemoglobin (11.9-14.6 g/dl), RDW: red cell distribution width (12.1-14.3%), WBC: white blood cells (4490-1268/uL), ANC: absolute neutrophil count (1900-7900/uL), ALC: absolute lymphocyte count (1300-3600/uL), AMC: absolute monocyte count (200-500/uL), MHR: monocyte/HDL ratio, Plt: platelet count (173-390 10^3/uL), MPV: mean platelet volume (9.1-11.9 fL), AST: aspartate aminotransferase (0-31 U/L), ALT: alanine aminotransferase (0-33 U/L), ALP: alkaline phosphatase (0-104 U/L), GGT: gamma-glutamyl transferase (6-42 IU/L), 25-OH-D: 25-hydroxy vitamin D (25-80 ng/ml). *: Independent Sample t Test, **: Mann-Whitney U test, Statistically significant data is shown in bold

In the patient group, grade 1 hepatosteatosis was found in two patients, grade 2 in one, and grade 3 in one patient, while the liver was of normal size and echogenicity in the ultrasonographic examination of four patients. In the control group, grade 1 hepatosteatosis was detected in one patient, grade 2 in two, and grade 3 in one patient, while normal ultrasonographic findings were observed in eight. Since the number of patients was small, and the number of grades was heterogeneous a statistical comparison could not be made.

While the mean of apo A1 levels evaluated only in the patient group was 99.4±50.8 and the median 116 (25th-75th 71.8-143) (laboratory reference range 104-163 mg/dl), the mean of apo B levels was 45.9±21 and median 38 (32.3-59.9) (laboratory reference range 60-117 mg/dl). While only apo B was low in five patients and only apo A1 was low in one patient, the deficiency of both was found in two patients. Genetic test results were not evaluated in this study.

Prothrombin time (PT) and international normalized ratio (INR) measurements, which were requested to evaluate vitamin K deficiency, were found to be at normal levels in the entire patient group.

DISCUSSION

In this study, laboratory data of eight patients with primary hypolipoproteinemia were compared with those of 12 healthy control participants. Apo A1 deficiency and low HDL consistent with hypoalphalipoproteinemia were found in one of the patients with primary hypolipoproteinemia, low LDL consistent with apo B deficiency, and heterozygous familial hypobetalipoproteinemia in five patients. In the other two patients, both apo A1 and apo B deficiency and both HDL, LDL, and TG were low, so familial combined hypolipidemia was considered. Genetic tests were not included in the study since it has not been performed on all patients yet.

As expected, TG, LDL, and TC levels were found to be low in the patient group. Although apo A1 deficiency and low HDL were detected in a total of three patients and mean HDL values were lower in the patient group, no statistically significant difference was found between the groups.

When Lp(a) levels were evaluated, significant Lp(a) elevation was observed in only one patient in the patient group. When this patient was excluded from the evaluation and the groups were compared, Lp(a) levels in both groups were found to be in the normal range, but statistically significantly lower in the patient group than in the control group. Lp(a) is an LDL-like lipoprotein. It can be said that it will be affected by LDL-C levels due to the component that shares structural and functional properties with LDL in its composition, therefore it may be low in patients with hypobetalipoproteinemia (9). It is also known that anti-sense oligonucleotides used in the treatment of dyslipidemia inhibit apo B synthesis and Lp(a) levels decrease with this treatment (10). When the literature was reviewed, it was stated in the publications that there was no difference in Lp(a) levels in patients with primary hypolipoproteinemia compared to healthy control groups (11-13).

In the current study, the patient excluded in the Lp(a) evaluation was also the patient in whom TG, HDL, and LDL were all low, and both apo A1 and apo B were found to be low and whose diagnosis was considered as possible familial combined hypolipidemia. The patient's Lp(a) level was 113.4 nmol/L. It has been reported that the Lp(a) levels of patients with familial combined hypolipidemia are not affected and they are not different from controls in terms of NAFLD (13). In this patient, contrary to the theoretically expected low levels, Lp(a) was found elevated. It is also interesting that the same patient was the only one in whom grade 3 hepatosteatosis was determined in the patient group. NAFLD can be seen in patients with familial combined hypolipidemia in homozygous individuals (1). Since the genetic analysis of the patient was not performed, further interpretation could not be made.

The present study showed that AMC and MHR were higher in patients with primary hypolipoproteinemia than in the healthy control group. Monocytes are cells that have an important part in the release of pro-inflammatory and pro-oxidant cytokines. They are involved in all stages of the progression of atherosclerotic disease (14). HDL is known to have a protective role in atherosclerotic diseases with its anti-inflammatory and antioxidant effects. MHR, which is an index that combines the hematopoietic system, which represents the inflammatory component, and the metabolic profile, has come to the fore in recent publications as a prognostic marker in cardiovascular diseases (15,16). High MHR has also been shown in conditions such as metabolic syndrome and NAFLD, which are thought to be closely related to atherosclerosis (17,18). To the author's knowledge, this is the first study to investigate MHR in patients with primary hypolipoproteinemia. Despite the small sample size and the heterogeneous nature of the patients included, high AMC and MHR levels are important findings of the current study.

When the patient and control groups were evaluated in terms of NAFLD, fatty liver was detected ultrasonographically in four patients (50% and 33.3%, respectively) in both groups. However, AST, ALT, ALP,

and GGT tests were at normal levels in all participants, and no difference was found between the groups. Intergroup comparisons for NAFLD are difficult because of the small sample size and the heterogeneous grades of hepatosteatosis.

CONCLUSION

In a patient with hypolipoproteinemia, secondary causes should be excluded first. It is important to evaluate patients for diseases, infestations, and malignancies that may cause malabsorption related to the gastrointestinal tract; also in terms of symptoms such as weight loss and night sweats due to occult solid and hematological malignancies, and to perform the necessary screening tests to exclude the malignancies.

Primary hypolipoproteinemias are rare conditions. Heterozygous familial hypobetalipoproteinemia, which is the most common genetic cause of low LDL, has been reported with a frequency of 1 in 10,000 (19). However, despite this rare incidence, it is a situation that clinicians should consider in the evaluation of lipid profile results, which are frequently done in every day routine, due to the potential complications that may occur and the potential to require genetic counseling. It is important to monitor patients with heterozygous familial hypobetalipoproteinemia for NAFLD (20). Since it is known that low LDL has a protective effect against atherosclerotic diseases, it can be assumed that patients with hypobetalipoproteinemia have a low cardiovascular risk. However, since there is insufficient data on the risk of atherosclerotic disease associated with low HDL in patients with hypoalphalipoproteinemia, these patients and their families should be carefully monitored due to the autosomal dominant inheritance pattern. With the prolongation of human life, it may be beneficial to monitor patients with hypolipoproteinemia in terms of cognitive dysfunction that may occur in the future.

Although patients with hypolipoproteinemia are attributed to a low risk for atherosclerotic diseases, high AMC and MHR, which are among the most important findings of the current study, are a warning that these patients should be followed carefully due to changes in lipid redistribution in terms of the risk of atherosclerotic disease, as well as the increased risk of NAFLD. Evaluation of this condition, which has not been examined in terms of MHR, which is accepted as an atherosclerotic risk indicator, with larger patient groups will contribute to a better understanding of hypolipoproteinemia and also the effects of lipid-lowering treatments on atheroinflammation. This work is a preliminary study in this respect.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskisehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 26.07.2022, Decision No: 35).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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